Using Epidemiologic Data to Evaluate Cancer Risk:

A Review and Meta-Analysis of Low-Level Arsenic Exposure in Drinking Water and Bladder Cancer

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Overview

- **Charge C2 to SAB: "Does the SAB agree that the Taiwanese dataset remains the most appropriate choice for estimating cancer risk in humans?"**
- **Relevant epidemiologic literature has been incompletely evaluated and considered**
- **Meta-analysis of bladder cancer and low-level arsenic exposure in drinking water, primarily from the U.S.**
  - No significant association observed
  - Models based on SW Taiwanese data tended to overestimate the meta-relative risks observed in our analyses, particularly for nonsmokers

Background

- **NRC and EPA risk analyses and dose-response models rely on data from SW Taiwan**
  - Lack of systematic discussion of studies from US and similar populations
  - Exclusion criteria applied to other epidemiologic studies not applied to SW Taiwan data
  - Limitations of SW Taiwan dataset largely ignored
    - Ecologic design
    - Bias and confounding
    - Generalizability to populations with low exposure
- **Uniform criteria should be applied to the review of all relevant epidemiologic studies**
- **Epidemiologic data from populations with low exposure to iAs are informative**

Objectives of Meta-Analysis

- **Meta-analysis of epidemiologic studies of low-level arsenic exposure in drinking water and bladder cancer**
  - Clarify association
  - Improve precision
  - Assess accuracy of models based on SW Taiwan data
- **Two questions:**
  - Is there a significant association between exposure to low levels of arsenic in drinking water and bladder cancer?
  - Are the relative risks (and meta-RR) from these epidemiologic studies within the range of **1.2 to 2.5** as would be predicted by the dose-response curves based on data from the Taiwan studies (NRC 2001, Table 5-3)?

Methods and Data Analysis

- **Inclusion/exclusion criteria for meta-analysis**
- **Eight studies eligible for meta-analysis**
  - Case-control or cohort studies of low-level exposure to iAs in drinking water and bladder cancer incidence (mortality)
- **Episheet used to calculate mRRs, confidence intervals, tests for heterogeneity**
- **Smoking status: Combined and stratified analyses**
- **Exposure category models:**
  - Collapsed exposure categories
  - All exposure categories
- **Additional analyses**
  - Sources of heterogeneity
  - Influence analyses

Results

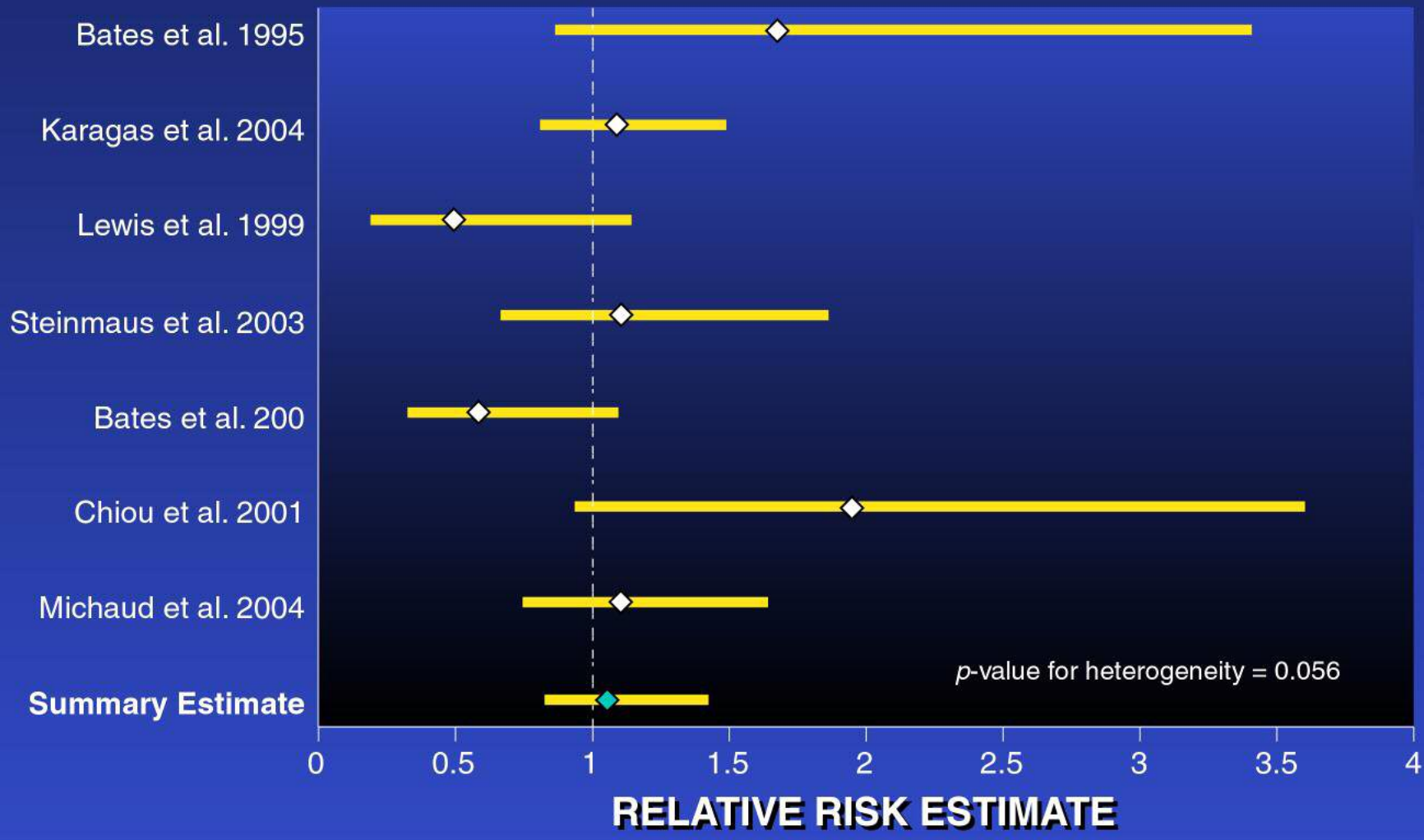
- See Table 2 and Figures 1–3 for summary of main results
- Appendices B, C for full results

Results (all studies)

	Smokers and Never Smokers Combined Collapsed Exposure Categories	Smokers and Never Smokers Combined All Exposure Categories	Never Smokers Collapsed Exposure Categories	Never Smokers All Exposure Categories	Ever Smokers Collapsed Exposure Categories	Ever Smokers All Exposure Categories
mRR 95% CI	**1.08** 0.82–1.43	**1.11** 0.95–1.30	**0.76** **0.52–1.12**	**0.81** **0.60–1.08**	**1.21** 0.88–1.66	**1.24** 0.99–1.56
P–Hetero-geneity	0.056	0.207	0.724	0.937	0.162	**0.032**
Number of Studies	7	8	5	6	5	6

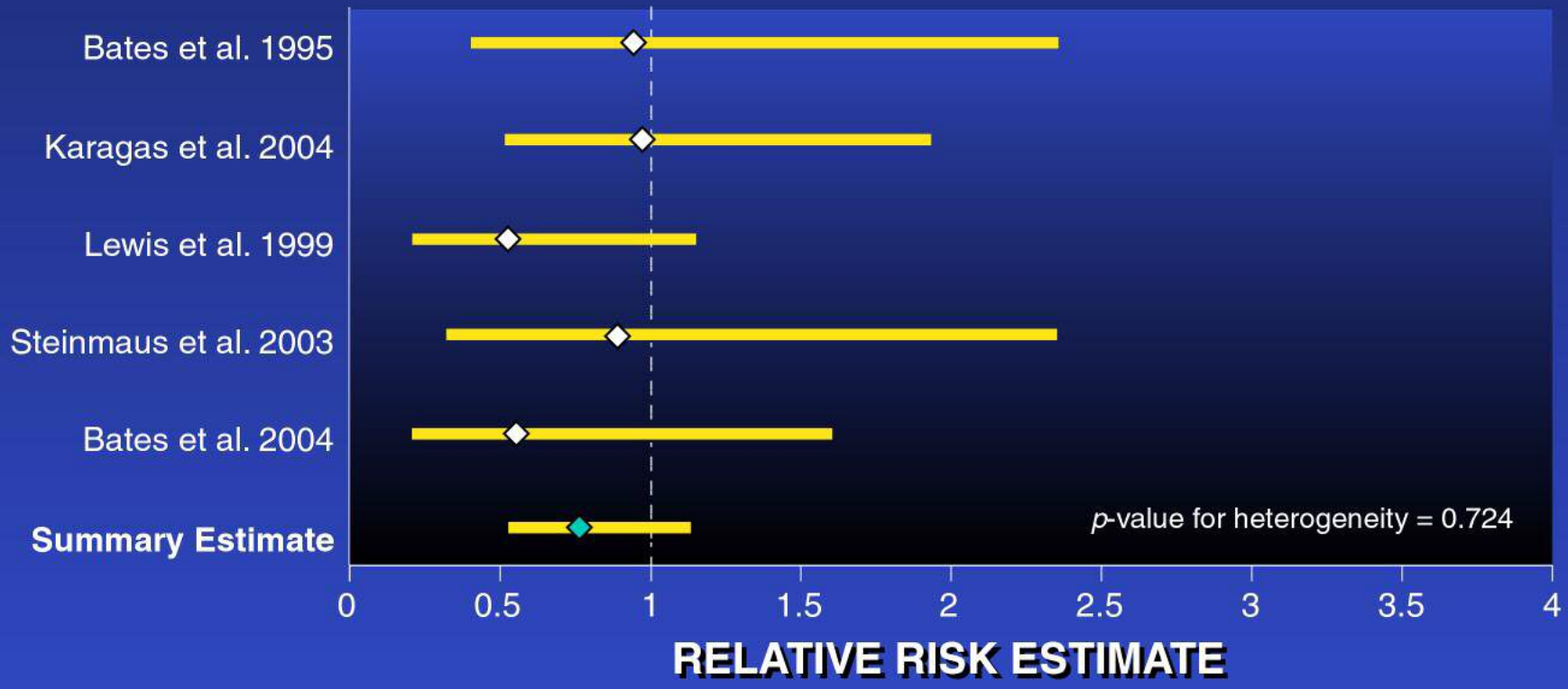
Source: Table 2, "Epidemiologic Studies of Low-level Arsenic Exposure in Drinking Water and Bladder Cancer: A Review and Meta-analysis"

Arsenic Exposure and Risk of Bladder Cancer: Collapsed Exposure Categories



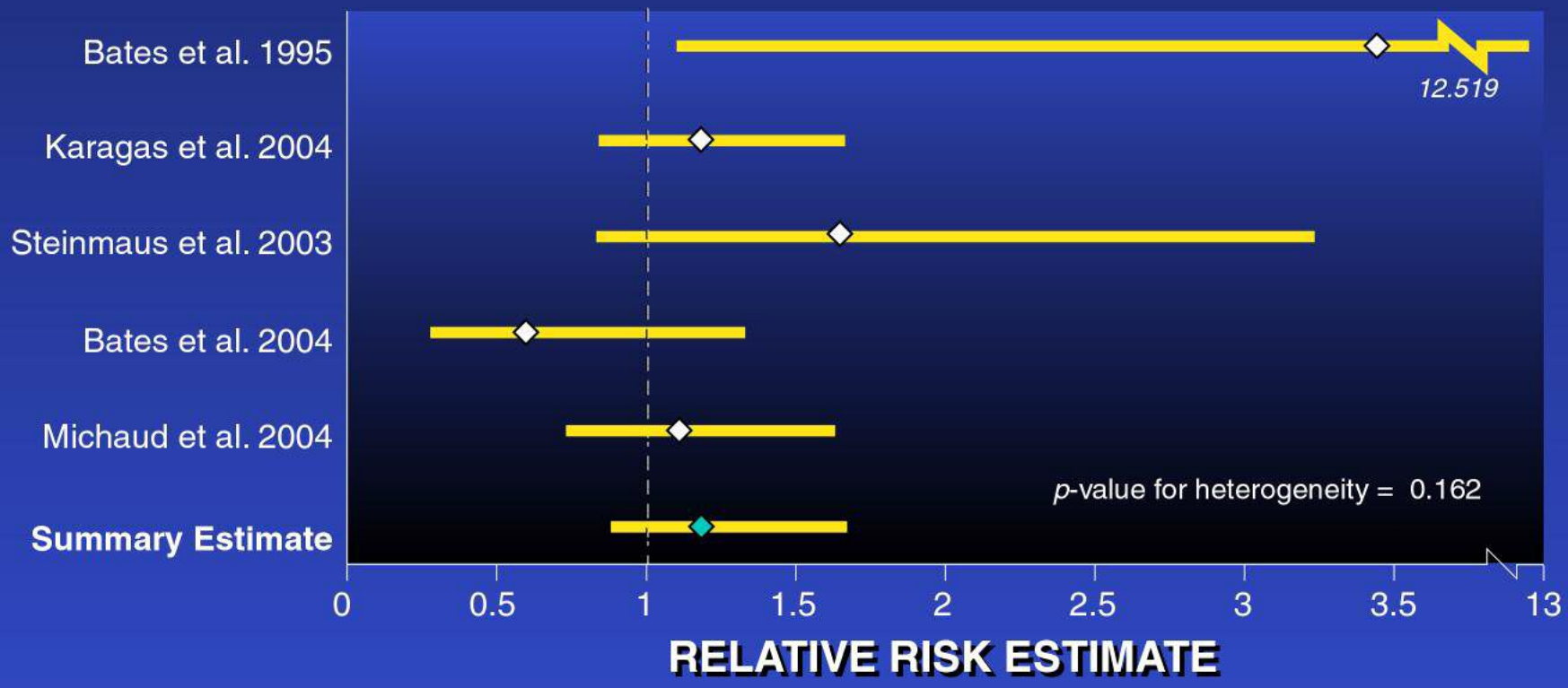
Source: Figure 1., "Epidemiologic Studies of Low-level Arsenic Exposure in Drinking Water and Bladder Cancer: A Review and Meta-analysis"

Arsenic Exposure and Risk of Bladder Cancer Among NEVER Smokers: Collapsed Exposure Categories



Source: Figure 2., "Epidemiologic Studies of Low-level Arsenic Exposure in Drinking Water and Bladder Cancer: A Review and Meta-analysis"

Arsenic Exposure and Risk of Bladder Cancer Among EVER Smokers: Collapsed Exposure Categories



Source: Figure 3., "Epidemiologic Studies of Low-level Arsenic Exposure in Drinking Water and Bladder Cancer: A Review and Meta-analysis"

Statistical Power

	Meta-Relative Risk	
	1.5	2.0
Ever + Never Smokers (n=7 studies)	0.91	1.00
Never Smokers (n=5 studies)	0.65	0.97
Ever Smokers (n=5 studies)	0.78	0.99

Source: One-sided test of significance (Hedges and Pigott, 2001)
Table 3, "Epidemiologic Studies of Low-level Arsenic Exposure in Drinking Water and Bladder Cancer: A Review and Meta-analysis"

Summary

- **Question 1: Bladder cancer was not significantly associated with low-level exposure to arsenic in drinking water**
  - Never smokers: mRRs were consistent, robust, and < 1.0
  - Ever smokers: Results were heterogeneous; no consistent evidence of increased risk or effect modification
- **Question 2: Main results of meta-analysis were not consistent with, and were below the range of RRs predicted by NRC (1.2 to 2.5)**
  - Majority of mRRs were less than 1.2
  - Results for smokers were variable

Conclusion

- Thus, the SW Taiwan dataset is inadequate for estimating cancer risk in U.S. populations exposed to iAs in drinking water

Thank You